STATE MEDICAID P&T COMMITTEE MEETING

FRIDAY, March 21, 2008
7:00 a.m. to 8:30 a.m.
Cannon Health Building
Room 125

MINUTES

Committee Members Present:

Lowry Bushnell, M.D.
Karen Gunning, Pharm. D.
Raymond Ward, M.D.
David Harris, M.D.
Jerome Wohleb, Pharm D.
Koby Taylor, Pharm D.
Duane Parke, R.Ph.

Board Members Excused:

Thomas Miller, M.D.
Kort DeLost, R.Ph.

Dept. of Health/Div. of Health Care Financing Staff Present:

Lisa Hulbert
Jennifer Zeleny
Tim Morley

University of Utah Drug Information Center Staff Present:

Chris Beckwith, Pharm. D.
John Vu
Linda Tyler, Pharm. D.

Other Individuals Present:

Craig Boody, Lilly
Barbara Boner, Novartis
Michele Puyear, Novartis
Elex Scheels, Novartis
Jon Beaty, Boehringer Ingelheim
Jennifer Swiechi, Daiichi Sankyo
Steve Scaerrer Daiichi Sankyo
Corbet Carver, Pfizer
Gerg Frei, Pfizer
Tony Molchan, Abbott
Sabrina Aery, BMS
Joann Ginal, BMS
Leo M. Stevenson, M.D.
Marty Daniels, Merck
Sean McGarr, Forest
Roy Palmer, Pfizer
Jim Ray, Pfizer
Mark Johnson, Daiichi Sankyo
Mark Germann, Novartis
Tim Hambacher, Abbott

Meeting conducted by: Karen Gunning, Pharm. D., Chairperson.

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1. Minutes for February were reviewed. Duane Parke made a motion to approve the minutes. Jerome Wohleb seconded the motion. The motion passed with unanimous votes from Dr. Bushnell, Karen Gunning, Jerome Wohleb, Koby Taylor, and Duane Parke.

2. DUR Board Update: Tim Morley addressed the Committee. There is no update at this time.

3. Combination Antihypertensives: Dr. Beckwith addressed the Committee. There are many fixed-dose combination antihypertensives on the market. The University of Utah Drug Information Service prepared two documents for this review. Combination products that have a combination of a thiazide diuretic + beta adrenergic blocker include bendroflumethiazide/nadolol, chlorthalidone/atenolol, hydrochlorothiazide/bisoprolol, hydrochlorothiazide/metoprolol, hydrochlorothiazide/propranolol. Combination products containing thiazide diuretic and angiotensin converting enzyme inhibitor include hydrochlorothiazide/benazepril, hydrochlorothiazide/captopril, hydrochlorothiazide/enalapril, hydrochlorothiazide/fosinopril, hydrochlorothiazide/lisinopril, hydrochlorothiazide/moexipril, and hydrochlorothiazide/quinapril. Combinations of thiazide diuretics and angiotensin receptor blockers include hydrochlorothiazide/candesartan, hydrochlorothiazide/eprosartan, hydrochlorothiazide/irbesartan, hydrochlorothiazide/losartan, hydrochlorothiazide/olmesartan, hydrochlorothiazide/telmisartan, and hydrochlorothiazide/valsartan. There are also combination thiazide diuretics with other antihypertensive agents, including chlorthalidone/clonidine, hydrochlorothiazide/aliskiren, hydrochlorothiazide/amiloride, hydrochlorothiazide/hydralazine, hydrochlorothiazide/methyldopa, hydrochlorothiazide/spironolactone, and hydrochlorothiazide/triamterine. Calcium channel blocker combinations include calcium channel blocker plus angiotensin converting enzyme inhibitor combinations, such as amlodipine/benazepril, felodipine/enalapril, and verapamil/trandolapril. There are also combinations of amlodipine plus angiotensin receptor blockers, including amlodipine/olmesartan and amlodipine/valsartan. There is also a combination of amlodipine with a non-antihypertensive agent, which is amlodipine/atorvastatin.

The main review looked at the question of whether fixed dose combinations improve patient adherence, compliance, or persistence. This is the question that was asked by the Medicaid P&T Committee. There are three important definitions to consider. Compliance is the degree to which patients do what they are told in following the medication regimen. Sometimes this may imply blame when the patients do not correctly follow the instructions. Adherence is similar to compliance, and some places will say that they are the same concept. Adherence also implies more cooperation or agreement between the patient and their practitioner. Persistence refers to continuation of therapy or the patient's likelihood of continuing therapy in the long term. In order to prepare this document, the Drug Information Service conducted a review of Medline, Cochrane, and AHRQ website, searching specifically for articles that evaluated these endpoints comparing fixed-dose combination products therapy with the individual components given as separate pills. They were able to find 171 titles in the initial search. Of those, 27 abstracts were retrieved and reviewed. Of those, 12 articles were reviewed, and 5 articles were used in the document that addressed these questions. They key clinical question, again, was do fixed-dose combination products improve compliance, adherence, or persistence in patients with hypertension compared to combination therapy with the individual components. Of the 5 published reports, one was a randomized controlled trial. There were 4 observational studies, and 1 meta-analysis. Two of the observational studies were published in one report. The one randomized controlled trial found no difference in compliance between the two treatment arms. By patient report, compliance was 51% with the fixed-dose product and 52% with the combination of the individual agents. By tablet count, it was 42% for the fixed dose product and 35% with the combination of the individual agents. This was not statistically significant. The largest report was a meta-analysis of observational follow-up studies. In that report, noncompliance was less likely with a fixed-dose combination at 36% compared to the individual components of 38%. Three of the individual observational studies that were included in the meta-analysis

found similar results. Persistence was increased with the fixed-dose product anywhere from 69-70% compared to 58% with the individual components. Adherence was also higher at 81-88% compared to 69-74% for the individual components. In one of the studies that was statistically significant for all age groups over 40. The difference between the two groups tended to get bigger as the patients got older. One of these studies found a difference in healthcare utilization between the two groups. They actually found decreased healthcare costs with the fixed dose products. However, patients in the individual components group were very much sicker at baseline, so it is difficult to tell whether that was a true difference, or it that was a function of how sick the patients were when they entered the study. In summary, fixed dose combination products may improve compliance, persistence, and adherence, although the available data are conflicting. One controlled trial found no difference. However, several observational trials found significantly higher rates of compliance, persistence, and adherence with the fixed dose products.

The second part of this discussion includes a table that lists the available products, as well as the dosage forms that they come in, the strengths, and whether or not a generic is available. This is available to the Committee as a reference.

Dr. Roy Palmer with Pfizer addressed the Committee. Caduet is Pfizer's combination product of the statin Lipitor and the calcium channel blocker amlodipine. It is a little different in that most of the combinations being considered today treat only one condition. Caduet treats both hypertension and high cholesterol in a single pill. The reason for that is that Caduet was designed to be a practical part of a drug regimen. These are two agents that are both well-known to physicians and two of the most widely prescribed cardiovascular agents. It makes sense to put them in a single pill, especially for patients on complicated multi-drug regimens. In terms of the evidence, there is a huge body of evidence for Lipitor with over 80,000 patients in 400 clinical trials. There are also numerous large-scale outcomes studies showing the benefit of amlodipine. In terms of its place in therapy, amlodipine is usually not given as first line therapy. The same is seen with Caduet. It is usually used as an add-on to patients who are already receiving a diuretic or ACE inhibitor. It is not promoted as a first-line drug. Both amlodipine and atorvastatin have long half-lives and good drug-drug interaction profiles, so that makes them ideally suited in a wide variety of different regimens. To summarize, Caduet is a very practical and simple approach for managing multiple risk factors. Utah Medicaid already covers atorvastatin and amlodipine. There is no financial downside to covering the combination product Caduet. One practical advantage may be one fewer dispensing fees and improved compliance. Preliminary studies done through managed care and compliance show a 2 to 3 fold increase in compliance with the single pill in patients already on multiple medications. For those reasons, the Committee is respectfully asked to consider including Caduet on the Preferred Drug List.

Dr. Michell Puyear of Novartis addressed the Committee. Diovan HCT and Exforge are part of the Diovan family, which was reviewed in the past. These products are approved for hypertension, although not approved for first-line treatment like many of the other combinations. The benefit of the combination products is potentially increased compliance and potentially decreased side-effects while still maintaining beneficial effects of the products. Diovan HCT does come in 5 fixed-dose combinations, has been studied in several clinical trials, including head-to-head studies versus a monotherapy component as well as in patients who were nonresponders to monotherapies. In these trials, patients achieved a statistically significant decrease in hypertension compared to monotherapy. It has been studied versus amlodipine in several studies as well. Patients experienced fewer adverse

events and discontinuations with Diovan HCT compared to amlodipine. Many times, patients have an increase in peripheral edema with amlodipine 10mg, but patients on the Diovan HCT were able to maintain positive blood pressure effects without the risk of peripheral edema. Exforge is different. It is an extension of the Diovan family that contains valsartan and amlodipine. With this combination, there are two products that are widely prescribed and well researched. Exforge is indicated for hypertension, but not first line. It comes in 4 different dosages. There have been head-to-head clinical trials versus the monotherapy components. In those studies, Exforge achieved statistically significant blood pressure reductions as compared to the components given as monotherapy. In a double-blind randomized multi-center trial, the efficacy of Exforge was evaluated not previously controlled on their antihypertensive. After 16 weeks of therapy, approximately 74% of the patients on the lower dose of 5/160 and 80% of the patients on the higher dose of 10/160 were at goal. It has been evaluated in difficult to treat patients as well and has achieved systolic blood pressure reductions of 43mmHg in African American patients, and up to 40mmHg in severe patients. It has been studied in patients with diabetes, obesity, systolic hypertension, and the elderly, and has demonstrated blood pressure reductions of approximately 30mmHg. A common side-effect with amlodipine 10mg can be peripheral edema. With patients receiving Exforge, patients have been able to achieve similar reductions as with amlodipine 10mg, but with fewer side-effects, and more patients have been able to remain on therapy. There is a black box warning for patients who are pregnant. This is common throughout the ARB class. Exforge and Diovan HCT offer advantage of combination products with increased compliance and potentially decreased side-effects, while still maintaining the blood pressure effects. Because of the favorable side-effect profile of both of these products, the Committee is respectfully asked consider both products for inclusion on the Utah PDL.

Dr. John Beatty from Boehringer Ingelheim addressed the Committee about Micardis HCT. This is a fixed-dose combination of telmisartan and hydrochlorothiazide available in three strengths. It is indicated for the treatment of hypertension. It is not indicated as a first-line agent. The antihypertensive effects of all 3 doses are maintained for the full 24-hour dosage interval. The antihypertensive efficacy of Micardis HCT versus valsartan HCT has been tested in approximately 1100 subjects with stage 1 and stage 2 hypertension comparing 80mg of telmisartan and 160mg of valsartan with 12.5mg of HCT given over 8 weeks. The mean reductions from baseline and seated trough measurements were determined at the end of the trial period and determined to be significantly lower in the telmisartan treated subjects. This study was reported almost two years ago. An almost identical study with a similar but different group of subjects was reported last January. The results were indistinguishable. In the MICAT 2 study, which was a community based trial of approximately 1600 subjects with either stage 1 or stage 2 hypertension who were either untreated or previously treated with monotherapy, subjects were started on 40mg of Micardis daily. After 2 weeks, if the JNC 7 goals wasn't reached they were titrated to 80mg of Micardis. Then they were titrated to 80mg of Micardis with 12.5mg of HCT if the JNC 7 goals were still not met. After a 10 week period, the average reductions in the mean 24 hour systolic and diastolic blood pressure in the entire cohort were about 11 and 6.5 mmHG. The mean reductions in seated office measurements were 20 and 11.5. Patients who were previously untreated had even greater mean seated office measurements. Patients who were previously treated with monotherapy and were switched to telmisartan HCT had mean 24 hour systolic and diastolic blood pressure measurement reduction of 8.2 and 5.0, while the corresponding mean seated office reductions were 6.8 to 10.3. Based on the ABPM criteria, blood pressure was fully controlled in 70% of all subjects. Based on seated office measurements, blood pressure was

fully controlled based on the JNC7 goals in 79% of all subjects. The fixed-dose combination of telmisartan and HCT have also been studied in patients with Type 2 diabetes, patients with chronic kidney disease, and patients over the age of 65. In comparator studies with telmisartan HCT versus valsartan HCT, for example, telmisartan was shown to be more effective as an antihypertensive in, for example, obese Type 2 diabetic patients. Like all RAS inhibiting patients, prescribing information for telmisartan HCT contains the FDA boxed warning to avoid prescribing during the second or third trimesters of pregnancy. There is no pediatric indication for the drug. The Committee is requested to consider the telmisartan HCT combination for inclusion on the Preferred Drug List.

Duane asked if an increase in side effects is seen with an increased in dose of the product. Broadly speaking, no. However specific information will be provided at a later time.

Karen Gunning asked what doses were studied in the telmisartan versus valsartan studies. The doses were 80mg of telmisartan and 12.5mg of hydrochlorothiazide versus 160mg of valsartan. The study was done before the 320mg dose of valsartan was approved. Dr. Beckwith asked if the doses were equipotent. Dr. Beatty did not know; however, the doses that were chosen for the study were the highest approved doses at the time.

Jennifer Swiecki of Daiichi Sankyo addressed the Committee. Benicar HCT is available in 3 different strengths. It is indicated for the treatment of hypertension, but not indicated as first-line therapy. In patients with stage 2 systolic hypertension, prospective open-label titration study evaluating the safety and efficacy of olmesartan medoxomil monotherapy and olmesartan and hydrochlorothiazide combination therapy showed a dose-dependant reduction in seated systolic and diastolic blood pressure when used either as monotherapy or in combination therapy. After a placebo run-in, patients were started on Benicar 20mg. After a three week intervals, they were titrated to Benicar 40mg, Benicar HCT 40/12.5mg, and Benicar HCT 40/25mg if their blood pressure was greater than 120/80. Patients exited the study, and the last measurement was carried forward if at any point a blood pressure below 120/80 was achieved. At week 12, the dose of olmesartan medoxomil and hydrochlorothiazide 40/25mg resulted in mean reductions of seated systolic and diastolic blood pressures of 35/14 mmHg respectively. This translated to a cumulative 70.4% of patients achieving a blood pressure goal of less than 140/90. Azor is a fixed-dose combination of amlodipine and olmesartan medoxomil and is indicated for the treatment of hypertension alone or in combination with other antihypertensive agents. Azor is not indicated for initial therapy of hypertension. It is available in doses of amlodipine either 5mg or 10mg and olmesartan medoxomil either 20mg or 40mg. An 8 week pivotal multicenter randomized double-blind placebo controlled parallel group study was designed to assess the efficacy and safety of coadministration of amlodipine plus olmesartan in adults with mild to severe hypertension. The mean baseline blood pressure was 164/102. It compared Azor to the respective monotherapies. The primary endpoint was the change with a mean change in seated diastolic blood pressure at week 8 from baseline. The results showed that each combination therapy had significantly greater reductions in seated diastolic and systolic blood pressure compared to the monotherapy components. Each active treatment had a statistically significant reduction in seated diastolic and systolic blood pressure from baseline to week 8 with last observation carried forward. Overall, the greatest reductions in seated blood pressure occurred in the groups treated with amlodipine 10mg plus olmesartan 40mg followed by the group treated with amlodipine 10mg plus olmesartan 20mg. The efficacy and safety of Azor was similar in patients both less than and greater than 65 years of age, and in patients with or without diabetes. Azor was also effective in treating Black patients. Azor

resulted in more patients being able to reach their respective JNC7 goals. 43-53% of these patients achieved their JNC goal on combination therapy compared to the respective monotherapies. As noted with other renin-angiotensin aldosterone blocking agents, Azor has a black box warning for pregnancy. The only adverse reaction that occurred in greater than or equal to 3% of patients was edema. Edema was proactively assessed in this trial, and as a result the observed incidences were higher than the reported incidences with amlodipine or Benicar. The P&T Committee is asked to allow patient access to Benicar HCT and Azor.

Dr. Mark Johnson, family physician from Taylorsville, addressed the Committee. He has been asked by Daiichi Sankyo and Forest to discuss Azor. He has used Azor in a number of patients. Hypertension is a difficult thing to get under control. Studies have shown that people need 3-4 medications to get their blood pressure to goal. Also, JNC7 guidelines recommend started with combination treatment or multiple agents if the blood pressure is over 20mmHg systolic or 10mmHg diastolic above the goal level. Compliance is always an issue, especially with more complicated drug regimens, multiple medications, etc. Combination therapy in these patients makes sense. Azor is one of the more potent antihypertensives to come along, being a combination of olmesartan and amlodipine. With the multiple dosage strengths, an average reduction of 24/14 is seen in the lower strengths, all the way up to 30/19 with the higher strengths. Also, in the pivotal studies it was shown to be equally effective or to have similar efficacy in special populations, such as obesity, diabetes, elderly patients, etc. Of interest, it has shown greater efficacy of up to a 40mmHg drop that started out with more severe hypertension. He pulled charts of some of the patients that he has had on it recently. It does perform as advertised, with getting 30-40 points of reduction in a variety of patients with different complexities. The first one got a 40mmHg drop when started on Azor 5/40mg. Other patients have achieved similar results. A blood pressure card of a patient that tracked was included. Azor is a very effective agent. It simplifies the drug regimen for many of these patients. It performs as outlined in the studies. The Committee is respectfully asked to include it in the Preferred Drug List.

Dr. Joann Ginal of Bristol Myers Squibb addressed the Committee. Because of the new indication on Avalide, she has requested that the new PI for Avalide be passed out at the conclusion of her summary. Avalide is irbesartan and hydrochlorothiazide in one tablet. The indications for Avalide are for treatment of high blood pressure for patients whose blood pressure is not adequately controlled on monotherapy. A new indication for Avalide is that it is now indicated for the treatment of high blood pressure as initial therapy in patients who are likely to need multiple drugs to achieve their blood pressure goals. This indication is consistent with the JNC7 guidelines that recommend that physicians consider starting with combination therapy for most patients in stage 2 hypertension that need moderate as well as severe systolic > 160 and diastolic > 100. Avalide is the first antihypertensive fixed-dose combination to have this broad indication for initial therapy. The approval is based on data that comes from 2 clinical trials including more than 1200 patients with moderate to severe high blood pressure. Patients treated with Avalide achieved significantly greater mean blood pressure reductions versus irbesartan or hydrochlorothiazide alone. In the severe hypertension studies, patients treated with Avalide also achieved more rapid and greater blood pressure control. The safety profile for Avalide as initial therapy is similar to that of irbesartan or hydrochlorothiazide monotherapy. An additional study in patients uncontrolled on monotherapy known as the INCLUSIVE trial evaluated the efficacy and safety of Avalide in 1005 hypertensive patients previously uncontrolled on monotherapy. It included 30% of patients with type 2 diabetes and 46% of patients that had metabolic syndrome. Looking at the 18 week trial, 69% of patients achieved blood pressure goals of 140/90 and < 130/80 for

hypertensive patients with diabetes. The study medications were well tolerated, and most adverse events were transient and mild or moderate and considered unrelated to the study medication. The most common drug-related adverse event was dizziness at 3%. As far as long-term studies, there was a pooled analysis of one year open label extensions of two multi-center placebo-controlled studies in which there were over 1000 patients with diastolic blood pressures of 95-110 mmHg. The long-term treatment of Avalide was considered safe and well tolerated. From months 2-12, at least 87% of patients were receiving Avalide without adjunctive therapy. A total of 7.5% of patients discontinued the study due to adverse events. The most frequent adverse events were fatigue at 0.8% and rash at 0.5%. The average absolute bioavailability of irbesartan is 60-80%, which is the most of any angiotensin receptor blocker. Peak plasma concentrations occur at 1.5-2 hours post oral administratiom. Elimination half-life is 11-15 hours, which makes irbesartan a true once-daily angiotensin receptor blocker. Food does not effect the bioavailability of irbesartan. In closing, Avalide is the first antihypertensive fixed-dose combination that is unique in its new indication for the treatment of hypertension as initial therapy in patients who need multiple drugs to achieve their blood pressure goals. Blood pressure reductions with Avalide were significantly greater than irbesartan or hydrochlorothiazide therapy alone. The safety profile of Avalide as initial therapy is similar to that of irbesartan or hydrochlorothiazide as monotherapy. The Committee was thanked for the consideration of Avalide on the PDL.

Dr. Leo Stevens addressed the Committee. Dr. Stevens is a physician from Ogden, UT. In September of this year, he will have completed 50 years in the practice of medicine. He has seen many changes. When he started in medicine, he was told that general medicine was no longer going to be viable, so he became a specialist in the field of obstetrics and gynecology. He has since given up doing inpatient work, so he is currently practicing office gynecology and internal medicine. Many of the patients that he had delivered and treated surgically are now hypertensive, have high cholesterol, hypothyroidism, have type 2 diabetes. Some have had malignancies and a variety of other conditions. As a physician who has had about 50 years in practice, he can remember when a diuretic became the drug of choice for hypertension. We have come a long way in treating many of these conditions. He can also remember when each disease state was compartmentalized, but now we have merged them all together since the body acts as a whole. As a physician, he also acts as a whole. When the patients come to the office, they wander through the maze of medicine looking for as much direction as they can get. One of the directions that they have in the office is samples of drugs. We can give patients samples, and give them directions on how to use it. One physician in general practice years ago did a study of how many patients actually filled the prescriptions that they were given. He had a waste basked by the door, and found that about 50% of the prescriptions that he wrote would end up in the waste basket as the patients exited the door. Dr. Stevens has prescribed many of the prescriptions that have been under discussion today, as well as generics. It is very time consuming to have to find a company's formulary. It is confusing to patients and frustrating to the office staff. Physicians practicing medicine should be allowed to practice medicine. They have gone from general physicians, to specialists, to pawns to an administration trying to provide care in a broad sense at a cheap price. We treat hypertension today than 50 years ago, so physicians should be allowed to practice medicine since that was what they were trained to do.

Karen Gunning stated that the first question of whether the Committee should recommend even paying for antihypertensive fixed-dose combinations should be addressed first. Dr. Ward stated that for some people it is easier to be on one tablet rather than two tablets, but that it sometimes becomes confusing for patients who don't know what active ingredients

are in the pills that they are taking. Dr. Bushnell agreed, and stated that he sometimes looks at a patient's complete medication regimen and realizes that they are being seriously overdosed on a particular ingredient, such as hydrochlorothiazide, because it is contained in a number of the medications that a patient is taking.

Karen Gunning stated that some of the issues that have been discussed in the P&T Committee are really more DUR issues. For example, HCTZ not being discontinued when moving a patient to a combination product. With some of these other combinations, there could be additional issues of a patient receiving multiple ARBS, multiple ACEs. This is a serious safety issue that Medicaid could address through the computer systems. In terms of the information presented from the evidence, it is not very strong. But we cannot say that there is no benefit to adherence and compliance. There is some value to paying for these combinations, and hopefully through safety measures taken by the DUR Board or with computer programming, some of the safety and confusion concerns could be addressed. The question should first be asked if Medicaid should even pay for combination products.

Dr. Ward stated that he feels that Medicaid should cover combination products. Many of his patients are on lisinopril/HCTZ combinations, they understand it, and it works well for them. From what Dr. Beckwith said, it is uncertain whether combination products are beneficial, especially with so many combination products available. The recommendation should be that they seem to be therapeutically equivalent. The Committee should not tie a physician's hands if a particular product is beneficial. The Committee should make a recommendation that the products are therapeutically equivalent, and where there are generics available or where the cost of the combination product does not exceed the cost of the single entity product that is already on the PDL that those combination products should be included.

Koby stated that for patients on the PCN plan who are restricted to four prescriptions per month, it is nice to have combination products available so that they can get all of their needed medications under the four prescription monthly limit.

Karen clarified that the ARBs currently on the preferred drug list are Diovan, Benicar, and Avapro. One of the key points of what Dr. Ward stated if there are combination products with the agents that are already on the PDL, they should be the ones that are covered rather than having combos that are different from the individual products that are on the PDL.

The Committee is looking at thiazides + beta blockers, thiazides + calcium channel blockers, thiazides + ACE inhibitors, thiazides + ARBs, thiazides + misc., calcium channel blockers + ARBs, and the newer amlodipine combinations. Caduet, the atorvastatin + amlodipine combination does not fit into this discussion at all, since it covers two classes and represents its own class. It is really a DUR Board drug issue, particularly since Karen has seen a number of instances where a patient has been getting Caduet plus a statin, she recommended that it not be included in the discussion. Karen asked Tim if it had been looked at by the DUR Board.

Dr. Harris stated that when he prescribes multiple antibiotics for MRSA, he gets incessant calls from the pharmacy asking if that is really correct. He wondered how a pharmacy would not call if a patient was receiving multiple agents with statins or hydrochlorothiazide. Karen said that she can only hope that it is because multiple pharmacies are involved.

Dr. Ward restated his motion that the P&T Committee finds that the combination

antihypertensive agents are therapeutically equivalent to their individual agents. Where there are generics available or where the cost of the combination product does not exceed the cost of the individual products on the PDL, the Committee recommends that the combination products be included on the PDL. Jerome Wohleb seconded the motion. The motion passed with unanimous votes from Dr. Bushnell, Karen Gunning, Jerome Wohleb, Koby Taylor, Dr. Harris, Dr. Ward, and Duane Parke.

4. Epleronone/Spironolactone: John Vu addressed the Committee. Both are aldosterone antagonists labeled for the treatment of hypertension and congestive heart failure. Epleronone is more specifically labeled for CHF post myocardial infarction. Spironolactone is also labeled for primary hyperaldosteronism, cirrhosis of the liver accompanied by edema and/or ascites, nephrotic syndrome, and hypokalemia. For this review the Drug Information Service focused mainly on the use for hypertension and CHF. The literature search that was conducted searched the Medline database, Cochrane library, and a reference list of articles. They included trials that had directly compared spironolactone and epleronone for hypertension or heart failure. When these individual trials were not available, meta-analyses or Cochrane systematic reviews that were available were included. If those were not available, individual trials with mortality endpoints were included when possible. When trials using mortality endpoints were not available, trials using active comparators with at least 100 patients were included. There were 346 articles identified through the literature search. 20 of these articles were pulled for further review, and 9 were included based on the inclusion criteria previously mentioned. There were 6 epleronone trials and 1 spironolactone trial that were included for hypertension, and 2 studies (1 spironolactone and 1 epleronone) that were included for heart failure. With the hypertension trials, 4 trials were included for epleronone that were monotheraphy trials. The aldosterone antagonists are generally used as adjunctive therapy for hypertension. Looking at the combination studies with epleronone and other agents such as ACEs or ARBs, there was a significantly greater reduction in systolic blood pressure. When epleronone was combined with an ACE or an ARB, the reduction was 13-16mmHg systolic, compared to an ACE or ARB monotherapy where the range of reduction was 7-9mmHg. A significant reduction in diastolic blood pressure was also observed with epleronone plus an ARB combination. This was a reduction of about 13mmHg compared to ARB therapy alone. There were no studies that evaluated spironolactone as add-on therapy for hypertension. The two trials that were included for heart failure both evaluated mortality endpoints. In both studies, there was a significant reduction in the incidence of death from cardiovascular causes. As far as adverse drug reactions, they cause similar types of adverse events. Hyperkalemia, gynecomastia, menstrual abnormalities, and impotence have been reported with both agents. There was a study that did compare serum potassium concentrations between spironolactone and epleronone, and there were smaller mean increases in serum potassium concentrations with epleronone 50-100mg per day compared to spironolactone 100mg per day. Increases in serum postassium between epleronone 400mg and spironolactone 100mg were similar. With epleronone, there may be a theoretical advantage as far as adverse drug reaction profiles go, because the agent is a more selective aldosterone receptor blocker than spironolactone; however, the data are insufficient to determine whether there is a more advantageous safety profile with either agent. With drug interactions, drugs that inhibit CYP3A4 may reduce epleronone metabolism, which, therefore, may increase serum concentrations and pharmacological effects of epleronone. Concomitant use with potent CYP3A4 inhibitors is contraindicated with epleronone. A dose reduction is recommended with weaker CYP3A4 inhibitors given in combination with epleronone. In summary, there are no published head-to-head trials comparing the efficacy of spironolactone with epleronone. Adverse events

reported are similar between the two. Spironolactone is available generically, while epleronone is not.

Karen stated that she highly doubts that these agents are used very much for the treatment of hypertension, and that the Committee is looking more at evidence-based use for the treatment of heart failure, for which these studies seem to have a little bit different population with a very similar outcome, in terms of both providing a benefit in terms of reducing mortality in patients with heart failure. Are there differences in the safety and efficacy of these drugs that would cause the Committee to recommend that Medicaid cover one over the other?

There was no public comment on this class of drugs.

Dr. Ward felt that from what Dr. Vu said, there was no way to tell differences in the safety and efficacy of these drugs. The report was pretty thorough, so he recommends that the Committee make a motion that the agents are therapeutically equivalent, and that the Board should decide which of these agents to include based on generic availability and cost. Dr. Wohleb seconded the motion. The motion passed with unanimous votes from Dr. Bushnell, Karen Gunning, Jerome Wohleb, Koby Taylor, and Duane Parke.

Next Meeting tentatively set for Friday, April 18, 2008. Next month, the Committee will be considering orally inhaled corticosteroids and leukotriene receptor agonists. Last month, Medicaid decided that for the short acting beta-agonist solutions for nebulizer, albuterol will be preferred. For the MDI's, albuterol and pirbuterol will be preferred. The branded albuterol inhalers will be allowed to stay on the PDL due to the imminent discontinuation of the non-HFA inhalers. For the long-acting beta agonist nebulizer solutions, formeterol and arformeterol will continue to be covered. For the MDI, salmeterol will be preferred. For the inhaled beta-agonist/steroid combinations both Advair and Symbicort product lines will be preferred.

Minutes prepared by Jennifer Zeleny